EPA uses risk assessments to identify and characterize potential threats to human health associated with exposure to pollutants. There are many uncertainties in the risk assessment process due to limitations in available data on pollutant sources and exposures. In addition, we are limited in our current understanding of the physical, chemical, and biological processes that relate human exposure, dose, and response. ORD supports EPA's mission to protect human health by conducting research to improve human health risk assessment and risk management.

Human Health Protection

ORD conducts human health risk assessment research to develop risk assessment methods to more accurately assess and characterize hazards from exposure to pollutants. This includes research on risks to the general population and to vulnerable groups such as children and communities that rely heavily on subsistence fishing, hunting, or farming.

ORD also spearheads research under the Food Quality Protection Act to ensure that pesticide residues on food do not pose a health hazard. Other ORD research provides the scientific foundation for regulatory decisions made under the Federal Insecticide, Fungicide and Rodenticide Act; the Federal Food, Drug, and Cosmetic Act; and the Toxic Substances Control Act. This chapter highlights recent ORD accomplishments in research to protect human health.

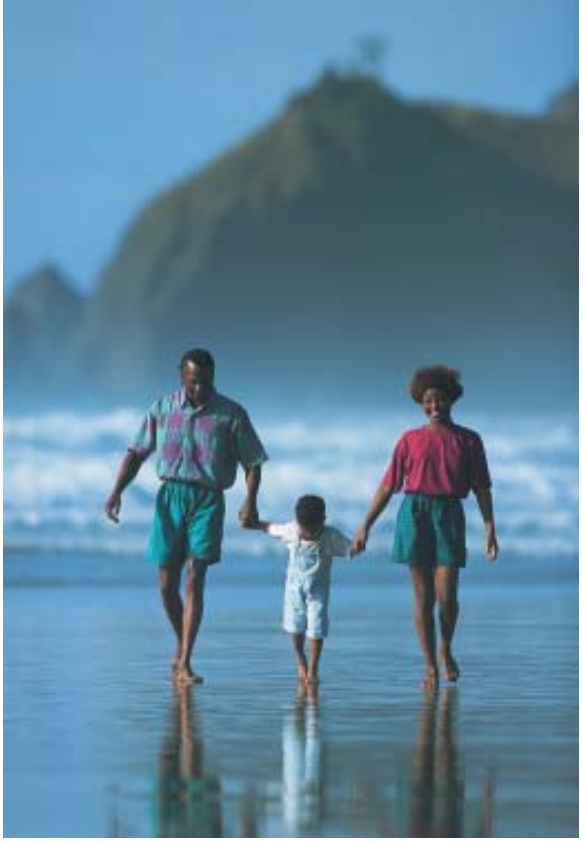
DIOXIN

Dioxin and related compounds are toxic chemicals formed as byproducts of combustion. They are widely distributed throughout the environment in low concentrations, persist in the environment, and accumulate in the body. Numerous animal research studies indicate that dioxin and related compounds can cause several types of cancer as well as reproductive failure and developmental problems. A growing body of evidence suggests that humans are similarly affected.

Dioxin Reassessment

Since 1991, scientists from EPA, other federal agencies, and the general scientific community have conducted a comprehensive reassessment of the human health problems caused by dioxin and dioxin-like compounds. In 2001, the reassessment passed its final peer review.

During the last few years, ORD scientists have made significant contributions to our



understanding of dioxin toxicity, mechanisms of action, and the sources of dioxin and dioxin-like compounds in the environment. ORD researchers developed methods for measuring dioxin dose and for relating those measurements to exposure; studied the assumptions and uncertainties underlying the current method for determining total dose when the situation involves simultaneous exposure to multiple individual dioxin-like compounds; applied innovative computer modeling techniques to identify the contributions of various dioxin sources to human exposure; and developed a user-friendly, widely accessible compilation of dioxin sources in the United States. This information was incorporated into the reassessment to provide a more accurate scientific understanding of the nature and extent of dioxin exposure and risk. EPA will use the revised dioxin risk assessment to develop a comprehensive risk management strategy. EPA will review the existing dioxin risk management efforts and, where appropriate, modify, expand, or redirect them to ensure that they are responsive to the scientific findings of the reassessment.

Dioxin and Reproductive Health

Historically, studies examining the potential association between dioxin exposure (from herbicides) in Vietnam veterans and neural tube defects (e.g., spina bifida) in their children have yielded conflicting results. Often, these studies had relatively few participants and might have been subject to sampling bias. Academic scientists funded by ORD are conducting a study that overcomes these shortcomings and examines the possibility that an interaction between dioxin exposure and a specific genetic anomaly may increase the risk of neural tube defects. To avoid sampling bias, the scientists contacted all Vietnam veterans for whom they could obtain a valid address. Those who parented a child with a neural tube defect and who agreed to participate in the study were asked to complete a questionnaire and provide a blood sample that was analyzed for dioxin and the genetic anomaly being investigated. A corresponding group of veterans whose children did not have neural tube defects will act as a control group for the study. By the end of 2001, 136 cases of veterans with affected children had been identified, from which 75 will be selected for participation in the study.

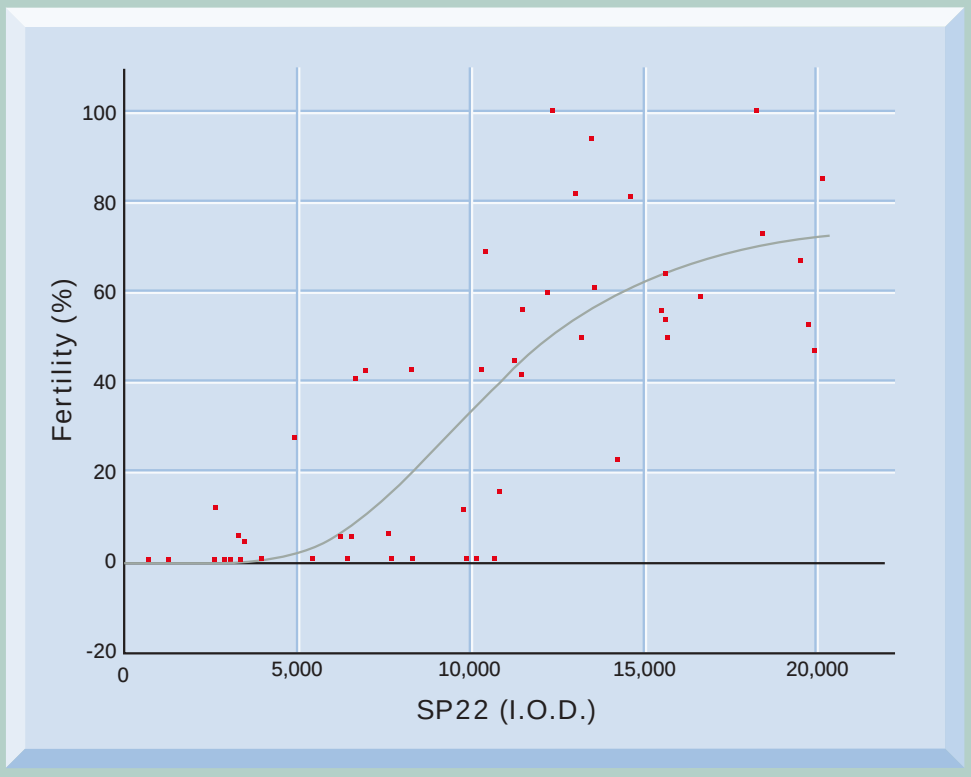
First EPA Biotechnology Patent

In 2001, an ORD scientist became the first EPA researcher to obtain a biotechnology patent on behalf of EPA. The patent is on the sperm protein SP22, the DNA nucleotide and amino acid sequence of SP22, and all recombinant fragments thereof. A second patent, covering the use of SP22 in fertility diagnostics and other reproductive technologies including contraception, artificial insemination, and *in vitro* fertilization, is pending.

The ORD scientist discovered SP22 while conducting rodent studies to identify molecular factors associated with infertility. When rodents were exposed to multiple chemicals known to cause infertility, levels of one sperm protein were consistently diminished. Furthermore, the amount of this protein was highly correlated with fertility. Because this sperm protein was 22 kilodaltons in size, it was named SP22. The data indicate that SP22 plays a critical role in the initial interaction of the sperm and egg during fertilization. Subsequent studies have used antibodies to SP22 to identify the location of SP22 on sperm from several species, including humans.

In this photomicrograph, sperm are attached to the zona pellucida surrounding the egg. Only one will penetrate the zona pellucida and fertilize the egg.

Preliminary data obtained from men with infertility of unknown cause show reduced SP22 levels, confirming that SP22 levels may be used as an indicator of male reproductive capability. An epidemiologic study is underway to determine if environmental exposure to varying levels of chemical byproducts formed during drinking water disinfection affect SP22 levels in human sperm.



The relationship between fertility and SP22 levels. SP22 is measured in integrated optical density units (I.O.D.).

PESTICIDES

Dermal absorption

Information on the absorption of chemicals through the skin is used to make decisions regarding pesticide registration. Many years ago, EPA scientists developed an *in vivo* rat protocol for evaluating the absorption of chemicals through the skin. Since that time, pesticide manufacturers have conducted over 300 dermal absorption studies using this protocol, which is the only validated method currently available. Scientists from ORD and EPA's Office of Pesticide Programs recently compiled 329 of these studies in a database. ORD researchers used this database to investigate how specific physical and chemical characteristics govern dermal absorption and to evaluate alternative methods for measuring dermal absorption. The scientists identified the key data elements needed to validate dermal absorption methods. They also evaluated previous validation studies for *in vitro* dermal absorption methods and found that these studies frequently lacked adequate concentration ranges and exposure times to compare the *in vitro* methods with the *in vivo* methods. Therefore, they concluded that current *in vitro* dermal absorption protocols have not been adequately validated. The dermal absorption database may be used to develop simulation models that predict the behavior of chemicals in the environment and their effects on people who work with pesticides or who come in contact with chemically contaminated soils.

In support of the Food Quality Protection Act, scientists at ORD and EPA's Office of Pesticide Programs are collaborating with academic scientists to develop methods, data, and models for evaluating children's cumulative exposure to pesticides. Results of an initial assessment indicate that exposure via skin contact and indirect ingestion may be high. Because data available to assess dermal and indirect ingestion exposure are limited, a draft protocol for measuring children's exposure to pesticides has been developed by ORD researchers. This protocol, which is currently being tested, provides approaches and methods to collect

exposure measurement data during field studies and to identify factors associated with exposure that are needed to improve assessments of dermal and indirect ingestion exposures.

Children's Exposure

ORD is collaborating with EPA's Office of Pesticide Programs and the National Center for Health Statistics to study pesticide exposure in children and adults through the current National Health and Nutrition Examination Survey (NHANES), which began in 1999. The study addresses two major questions:

- *What is the baseline national exposure to common pesticides in the United States?*
- *Do pesticide exposure levels vary according to age?*

The study includes a screen for organophosphate pesticides in the urine and measurement of urinary concentrations of 32 nonpersistent pesticides or pesticide metabolites. Approximately 2,500 samples will be analyzed, half from children age 6 to 11 years and half from persons between 12 and 59 years of age. Data collection was completed in 2001 and the National Center for Health Statistics plans to release the analyzed data on levels of pesticides by late 2002.

Repeated Exposure to Chlorpyrifos

While the health problems associated with short-term exposure to high doses of pesticides have been studied fairly well, the adverse consequences of chronic exposure to lower pesticide levels has not been thoroughly investigated. ORD researchers and academic collaborators are studying long-term exposure of rats to the organophosphorous pesticide chlorpyrifos. The primary purpose of the study is to determine what, if any, health problems may be caused by chronic exposure and what pattern of exposure is most harmful. The scientists also hope to learn if chlorpyrifos must enter the brain and spinal cord to cause harm or if

chlorpyrifos in the body and peripheral nerves, but not in the brain and spinal cord, can cause health problems. In 2001, the exposure phase of the study was completed and end-of-exposure assessments were conducted. The results will be reported at scientific meetings and in peer-reviewed journals and EPA reports.

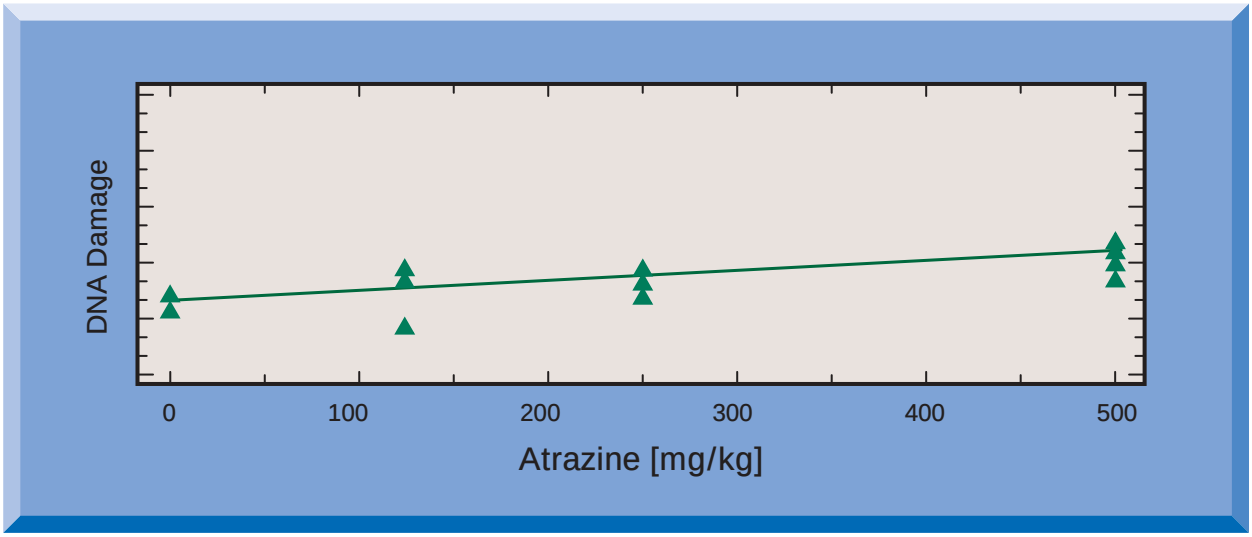
The use of chlorpyrifos by homeowners and in schools, parks, and other settings where children may be exposed was canceled effective December 31, 2001. However, the findings from the chlorpyrifos research may be important for assessing residential exposure to other pesticides.

Atrazine Mode of Action

Atrazine is a widely used herbicide that has been linked to mammary tumors in one strain of female laboratory rat. In the United States each year, an estimated 68 to 72 million pounds of atrazine is used to control annual grasses and

broadleaf weeds, primarily in the cultivation of food crops and evergreen trees. In the heavily farmed Midwest, many drinking water sources, including groundwater, contain atrazine and similar herbicides. The fact that atrazine induced mammary tumors in laboratory animals raised concerns about potential health problems in humans.

Evidence from earlier studies pointed toward a hormonal mechanism of causing



Relationship between DNA damage and dose of atrazine.

cancer that is unique to the one strain of rat. However, many compounds that cause cancer damage the DNA of cells, a phenomenon called genotoxicity. Previous *in vitro* and *in vivo* studies of atrazine's potential for genotoxicity produced conflicting results, which prompted ORD scientists to conduct experiments to determine conclusively if atrazine is genotoxic. They found that atrazine caused only slight DNA damage at very high doses.

Pesticide Risk Modeling System

ORD released a new version of the Exposure Analysis Modeling System (EXAMS) in September of 2000. EXAMS is a site-based, interactive computer program that constructs simulation models of aquatic ecosystems. It rapidly evaluates the fate, transport, and concentrations of synthetic organic chemicals such as pesticides, industrial materials, and substances leached from waste disposal sites. EXAMS offers a scientifically sound approach to characterizing the element of risk (directly to aquatic resources, and indirectly to humans through fish and shellfish consumption) posed by pesticide contamination of freshwater, estuarine, and marine ecosystems.

In 2001, ORD scientists designed and published methods to measure how reliably simulation models predict exposure to pollutants.

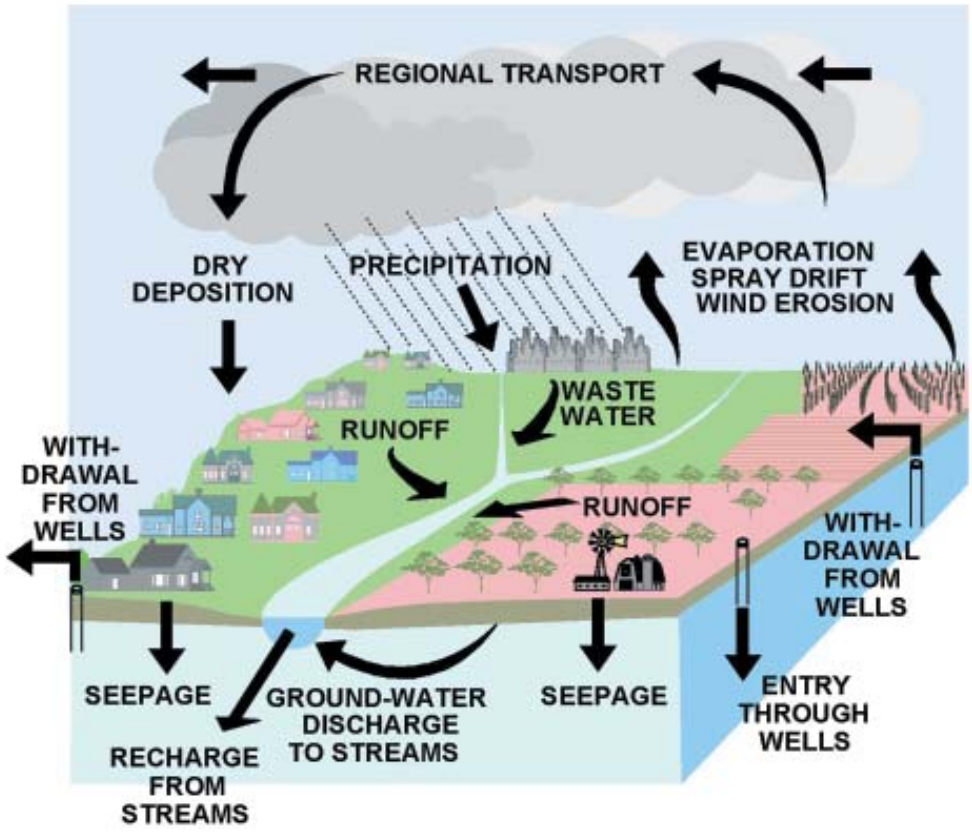


Diagram of major factors to include when modeling pesticide risk.

In related work, ORD researchers are developing a climatological database, including 30 years of data from 239 U.S. weather stations, to provide simulation models with a single, unified source of high-quality data covering a full range of weather factors that affect pesticide exposure.

3MRA MODELING SYSTEM

In 1999, ORD and EPA's Office of Solid Waste distributed Version 1.0 of a new site-based risk assessment modeling system.

The 3MRA system is a state-of-the-science environmental modeling technology that can simulate

- *Multimedia (air, water, soil, sediments),*
- *Multipathway (e.g., food ingestion, water ingestion, soil ingestion, air inhalation),*
- *Multireceptor (e.g., resident, farmer, gardener, fisherman, ecological populations) exposure scenarios for*
- *Risk (human cancer risk and noncancer effects, ecological population and community effects)*
- *Assessment (strategy used to provide information for regulatory decisions).*

Methylmercury Reference Dose

The oral reference dose (RfD) is an estimate of an oral daily dose that humans (including sensitive people) could ingest without an appreciable risk of noncancer, nonmutagenic* health problems during a lifetime. This estimate has some uncertainty spanning perhaps an order of magnitude. In general, doses less than the RfD are not likely to be associated with health problems, and are therefore less likely to be of regulatory concern. However, it is not appropriate to conclude that all doses below the RfD are risk-free or that all doses in excess of the RfD will cause health problems.

In 2001, ORD scientists completed the work necessary to assign an RfD for methylmercury, which causes developmental neuropsychological disorders to children exposed *in utero*. The primary source of ingested methylmercury is contaminated fish. The methylmercury RfD workgroup evaluated data from epidemiologic, human clinical, and laboratory toxicologic studies and other scientific reports to establish an RfD for chronic oral exposure of 0.0001 mg/kg of body weight per day. Also, the workgroup identified several areas that require additional research and/or analysis: cardiovascular effects, persistent and delayed neurotoxicity, and reproductive effects.

* *Because of the cellular mechanisms that lead to cancer development and that cause genetic mutations, theoretically, there is no threshold below which exposure to a carcinogen or mutagen is considered to be without risk. However, RfDs can be derived for the noncarcinogenic and/or nonmutagenic effects of substances that also cause cancer or genetic mutations.*

3MRA was initially developed to support the Hazardous Waste Identification Rule, which is an important regulation that defines when wastes are hazardous and subject to regulation under the under the Resource Conservation and Recovery Act. A major application of 3MRA is to pinpoint the level at which a waste is classified as hazardous for management and disposal purposes. 3MRA is a flexible risk assessment tool that can be applied to other waste programs and used to answer increasingly complex risk questions. In fact, the potential applications are so broad that EPA signed a Memorandum of Understanding with the Nuclear Regulatory Commission, Department of Energy, Department of Defense, U.S. Geological Survey, and U.S. Department of Agriculture, creating a common infrastructure for risk assessment technology development. These agencies have similar technology needs and this Memorandum will prevent unnecessary duplication of effort and promote development of a single technology that can be used by all these agencies.

LOOKING TO THE FUTURE

Anticipated accomplishments in human health research include

- *a summary of the methods available for assessing aggregate exposure to multiple pesticides and the effects of such exposures,*
- *innovative technology for data collection and low-cost exposure measurement methods to be used for studying children's exposure to pesticides,*
- *publications on the susceptibility of asthmatic children to combustion-related pollutants in seven communities,*
- *identification of common mechanisms by which pollutants cause different health problems, and*
- *a state-of-the-science report on how aging relates to risk assessment.*